



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Zheng J. Li, et al. :

APPLICATION NO.: 10/652,933 : Examiner: PESELEV, ELLI

FILING DATE: 08/28/2003 : Group Art Unit: 1623

TITLE: CRYSTAL FORMS OF AZITHROMYCIN:

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER RULE §132

I, Bruno C. Hancock, declare that:

1. I received my Ph.D. in Pharmaceutical Technology from the University of Bradford in the United Kingdom in 1991. Since then, I have been doing research in drug material interactions and surface phenomena of drug particles. I am currently a Research Fellow at Pfizer-Groton in Connecticut. I am an elected Fellow of the American Association of Pharmaceutical Scientists, a designation which recognizes scientific achievement in the pharmaceutical sciences.

2. I supervised the group that performed Brittle Fracture Index and Tensile Strength tests on various azithromycin crystal forms, including azithromycin monohydrate hemi-ethanol solvate and an azithromycin sample containing about 51% azithromycin monohydrate hemi-ethanol solvate (with the remainder being other azithromycin crystal forms, such as azithromycin monohydrate hemi-isopropanol solvate). The testing results are summarized in Table 1.

Table 1. Indices of Tableting Performance


Crystalline azithromycin samples	Brittle Fracture Index (BFI)	Tensile Strength (MPa)
About 51% pure azithromycin monohydrate hemi-ethanol solvate (unmilled with a median particle size of about 82 $\mu\text{m}$ )*	0.05	0.75
Azithromycin monohydrate hemi-ethanol solvate (unmilled with a median particle size of about 30 $\mu\text{m}$ )	0.37	1.62
Azithromycin monohydrate hemi-n-propanol solvate (unmilled with a median particle size of about 82 $\mu\text{m}$ )	0.11	0.69
Azithromycin monohydrate hemi-isopropanol solvate (unmilled with a median particle size of about 50 $\mu\text{m}$ )	0.10	0.79
Azithromycin dihydrate (milled on Fitzmill, .027" screen, knives, medium speed, with a median particle size of about 30 $\mu\text{m}$ )	0.10	0.99

\* The remainder being various other azithromycin crystal forms, such as azithromycin monohydrate hemi-isopropanol solvate.

3. Table 1 shows that the Tensile Strength of the azithromycin monohydrate hemi-ethanol solvate is higher than that of 51% pure azithromycin monohydrate hemi-ethanol solvate (1.62 vs. 0.75). A tensile strength greater than 1.5 MPa is desirable, particularly for drugs, such as azithromycin, which have a high dose (250mg or more per tablet) and must have relatively high loading in a tablet. Although the Brittle Fracture Index of the azithromycin monohydrate hemi-ethanol solvate is higher than that of 51% pure azithromycin monohydrate hemi-ethanol solvate (0.37 vs. 0.05), it is within the acceptable range.

4. Based on the totality of the testing data in Table 1, it is my opinion that the claimed substantially pure azithromycin monohydrate hemi-ethanol solvate possesses superior properties for tableting over non-substantially pure azithromycin monohydrate hemi-ethanol solvate (from Singer and Garcia) as well as over azithromycin monohydrate hemi-n-propanol solvate, azithromycin monohydrate hemi-isopropanol solvate and azithromycin dihydrate.

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

  
Bruno C. Hancock

29th August 2005  
DATE